EXHIBIT A

Selective Progesterone Receptor Modulators (SPRMs)

A Novel Therapeutic Concept in Endometriosis

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ABSTRACT: Endometriosis, the presence of endometrial tissue outside the uterus, is a progressive, estrogen-dependent disease and occurs nearly exclusively in menstruating women of reproductive age. Pain syndrome, however, represents the major clinical problem of this disease, manifested as dysmenorrhea, pelvic pain, lower abdominal pain, and dyspareunia. The manifestation of the disease, that is, the pain syndrome, rather than the disease itself currently represents the major indication for both the medical and surgical therapies of endometriosis. The major drawbacks of current medical therapies of endometriosis are sometimes severe side effects. In this review, selective progesterone receptor modulators (SPRMs, mesoprogestins) as a potential therapeutic concept in endometriosis are discussed. Due to endometrial selectivity and favorable pharmacological profile, SPRMs may have advantages over the current medical treatments of this disease. Other emerging therapeutic approaches for this disease are also mentioned.

KEYWORDS: endometriosis; SPRMs; ovulation; therapeutic; treatment

INTRODUCTION

Endometriosis, the presence of endometrial tissue outside the uterus, is a progressive, estrogen-dependent disease, which occurs nearly exclusively in menstruating women of reproductive age. The ectopic endometrium usually responds to changes in ovarian steroids, estrogen and progesterone, in terms of proliferation, differentiation, and bleeding. Increased angiogenesis and local inflammatory reaction are typical morphological changes in the endometriotic lesions.[1] Patients with endometriosis may present many different symptoms. Pain syndrome, however, represents the major clinical problem of this disease, manifested as dysmenorrhea, pelvic pain, lower abdominal pain, and dyspareunia.[2] In some women, the ectopic endo-

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metrium becomes highly invasive and forms so-called deep lesions, which often cause severe pain,[3] but the exact mechanism of pain in endometriosis is still unclear. It is believed that endometriosis-associated pain is caused by a local inflammatory reaction, which exacerbates during the perimenstrual period.[4] Since nonsteroidal anti-inflammatory drugs are effective in the treatment of endometriosis symptoms,[5] prostaglandins may play an important role in the pathogenesis of endometriosis-associated pain.

The manifestation of the disease, that is, the pain syndrome, rather than the disease itself currently represents the major indication for both the medical and surgical therapies of endometriosis. The major goal of the current medical treatment of endometriosis is to create an acyclic, hypoestrogenic environment by blocking ovarian estrogen secretion (GnRH agonists and antagonists; GnRH-a), by inducing pseudopregnancy, or by locally inhibiting estrogenic stimulation of the ectopic endometrium (progestins, androgenic progestins). Although all major therapies are effective for the treatment of pain, no single treatment seems to be superior in terms of efficacy.[5] The major drawbacks of the current medical therapies of endometriosis are sometimes severe side effects. The side effects of GnRH-a are due to an induced hypoestrogenic state, which adversely affects the skeletal and urogenital systems, while producing vasomotor symptoms at the same time. The major side effects of chronically administered progestins include breakthrough bleeding, bloating, breast tenderness, and mood changes. Chronic treatment with androgenic progestins such as danazol and gestrinone is often accompanied by seborrhea, acne, hirsutism, and negative changes in lipid profiles. Some androgenic side effects of danazol and gestrinone such as deepening of the voice, hirsutism, and clitoral hypertrophy are potentially irreversible. Hence, improvement of the profile of side effects should be considered a chief objective of new therapies of endometriosis.

In this brief review, we discuss the selective progesterone receptor modulators (SPRMs, mesoprogestins) as a potential therapeutic concept in endometriosis. Due to endometrial selectivity and favorable pharmacological profile, SPRMs may have advantages over the current medical treatments of this disease. We also comment on other emerging therapeutic approaches for this disease.

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (SPRMs, MESOPROGESTINS)

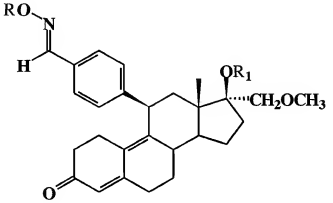
SPRMs are defined as a new class of progesterone receptor (PR) ligands, which exhibit both progesterone agonistic and antagonistic activities *in vivo*.[6] FIGURE 1 shows the chemical structures of the best-known SPRMs, J867, J956, J912, and J1042, synthesized and characterized at Jenapharm GmbH and Co. K.G. (Jena, Germany).

Like progestins and progesterone antagonists (antiprogestins), SPRMs show high-binding affinity to PR (TABLE 1). When compared to either progestins or progesterone antagonists (antiprogestins), the SPRMs, however, exert markedly different effects in various animal models. In the absence of progesterone, the SPRMs act like weak progestins. In the presence of progesterone, they may also show weak antiprogestagenic properties in some tissues, particularly in the endometrium. In marked contrast to progesterone antagonists, SPRMs show only a slight labor-inducing activity in pregnant animals (TABLE 1). FIGURE 2 schematically shows the graded

TABLE 1. Studies of relative binding affinities (RBA) and ED_{50} of labor-inducing activity of SPRMs in pregnant guinea pigs

Compound	RBA (%)		Labor-inducing activity (ED_{50}) (mg/animal/day)
	PR	GR	
RU 486	506	685	3.8
Onapristone	22	39	~3.0
J867	302	78	>100
J956	345	154	20
J912	162	76	>100
J1042	164	42	≫100

NOTE: The guinea pigs were treated sc on pregnancy days 43–44; autopsy pregnancy, day 50. PR (rabbit uterus): progesterone = 100%. GR (rat thymus): dexamethasone = 100%. Modified from reference 6, with permission from *Steroids* (one typing error corrected).



compound	R	R_1	
J 867	H	CH_3	oxime
J 912	H	H	17β-hydroxy oxime
J 956	$CONHC_2H_5$	CH_3	oxime (ethyl carbamate)
J 1042	$COSC_2H_5$	CH_3	oxime (ethyl thiol carbonate)

FIGURE 1. Chemistry of progesterone receptor modulators (SPRMs, mesoprogestins). These compounds are 11β-benzaldoxime-estra-4,9-diene derivatives.

progesterone agonistic and antagonistic activities in various animal models discussed below. The "pure" progesterone antagonists, onapristone and ZK 230 211,[7] are presented on the left side of this scale. These compounds do not show any progesterone agonistic activity. Progesterone and the pure synthetic progestin, R 5020, represent PR agonists with maximum progestagenic effects *in vivo*. Although some agonistic activities of RU 486 have been previously described,[8,9] this compound acts predominantly as a progesterone antagonist *in vivo*, particularly during pregnancy.[10,11]

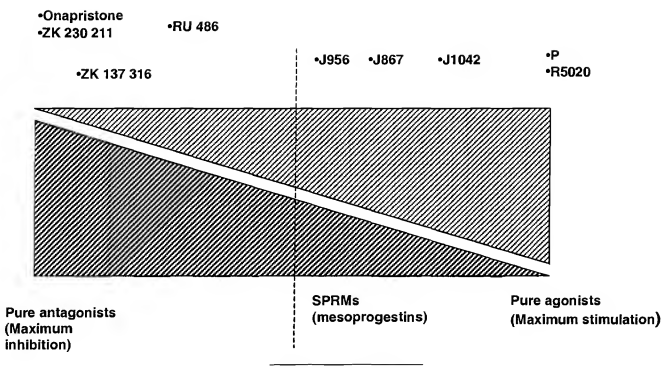


FIGURE 2. Spectrum of antagonistic and agonistic activities of PR ligands in *in vivo* animal models (guinea pigs, rabbits, rats).

The SPRMs are placed in the middle of this scale. J1042 is the strongest PR agonist of all J-compounds evaluated to date.[6]

Other hormonal activities: The SPRMs presented in FIGURE 1 exhibit a reduced binding affinity to glucocorticoid receptors (GR) compared to RU 486 (TABLE 1), which corresponds to marginal antiglucocorticoid effects of these compounds *in vivo*. They virtually do not bind to estrogen receptors (ER) and have no estrogenic activity *in vivo*.[6] At high doses, they show some mixed androgenic/antiandrogenic activities in rats.[6]

Effects of SPRMs on the Rabbit Uterus

The mixed progesterone agonistic/antagonistic activities of SPRMs are clearly evident in the juvenile, estrogen-primed rabbit uterus. This classical bioassay (McPhail test) has been frequently used to characterize both progestagenic and antiprogestagenic activities (FIG. 3, panels a and b).

In the rabbit uterus, progesterone stimulates proliferation and differentiation of epithelial endometrial cells, an effect that can be semiquantitatively assessed with a McPhail score. By definition, progesterone induces maximum stimulatory effects in this model (McPhail score 4). In the absence of progesterone, the SPRMs show a pronounced agonistic activity in the rabbit uterus (FIG. 3a). The stimulatory effects of SPRMs, however, are weaker than those of progesterone. Importantly, increasing the dose cannot enhance these effects. In the presence of progesterone, SPRMs exhibit some antagonistic activity (FIG. 3b). This activity, however, is significantly less than that of various progesterone antagonists such as mifepristone and other compounds such as onapristone, lilopristone, ZK 137 316, and ZK 230 211, which completely antagonize progesterone effects in this model (not shown). In analogy to the agonistic activity, increasing the dose does not enhance SPRM antagonistic effects. Importantly, RU 486 acts in this model as a "pure" progesterone antagonist, showing no agonistic activity at all. Similarly, other potent progesterone antagonists such as onapristone and ZK 137 316 do not exhibit progesterone agonistic activity in the rabbit uterus (not shown). The dose-response curves for both agonistic and antagonistic activities indicate that SPRMs stabilize the function of PR at an intermediate activity level in the rabbit uterus.

Effects of SPRMs in Pregnancy Models

The tissue selectivity of SPRMs is clearly evident in pregnancy models. SPRMs fail to maintain pregnancy in ovariectomized pregnant rodents such as mice and rats due to the fact that they have only partial progesterone agonistic activity. Yet, in rats and guinea pigs, the SPRMs inhibit both endometrial receptivity and implantation acting, in a manner similar to progesterone antagonists.[6] During early pregnancy, SPRMs act predominantly on the endometrium by inhibiting the decidual reaction and (most likely) other PR-dependent events.[6]

During advanced pregnancy, when the myometrium and cervix are the major target tissues for progesterone action, the SPRMs show only marginal effects in terms of induction of parturition or cervical ripening. The dissociation between endometrial and myometrial/cervical effects was most clearly observed in pregnant guinea pigs. Pregnant guinea pigs are considered a relevant animal model of human abortion and parturition.[12,13] The similarities between the guinea pig model and

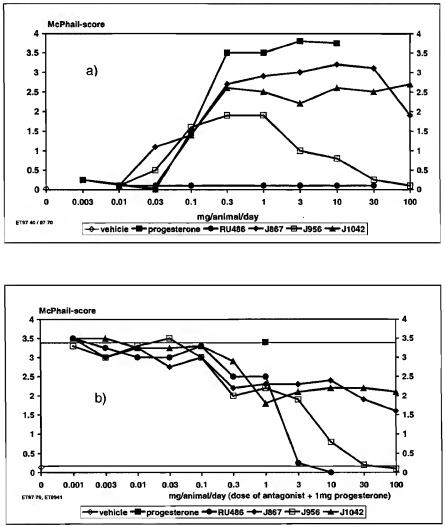


FIGURE 3. The PR agonistic (**a**) and antagonistic (**b**) activities of selective progesterone receptor modulators (SPRMs, mesoprogestins) in infantile estrogen-primed rabbits (modified McPhail assay). The juvenile rabbits were primed for 6 consecutive days with estradiol benzoate (5 μg/animal/day, sc). The PR ligands were then administered sc for 7 consecutive days. At 24 hours after the last injection, the uteri were collected for morphological evaluation. The assessment of stimulatory/inhibitory effects was performed according to the McPhail score (0 = no progestagenic activity; 4 = maximum progestagenic activity). (**a**) Agonistic activity of SPRMs. In this experiment, the animals were treated with the SPRMs only. (**b**) Antagonistic activity of SPRMs. The rabbits were treated with SPRMs in the presence of progesterone (1 mg/animal/day). Note that the threshold for agonistic activity of some of the antagonists is below that of progesterone. (From reference 6, with permission from *Steroids*.)

human pregnancy were also extensively discussed by Van Look and Bygdeman.[10] In this model, the progesterone antagonists such as mifepristone, onapristone, and lilopristone are very potent in inducing abortion or preterm parturition, which is brought about by both induction of labor and cervical ripening.[12–14] In marked contrast to these progesterone antagonists, both J867 and J956 have only marginal labor-inducing (abortifacient) activity in this model, irrespective of the dose.[6] Another structurally similar mesoprogestin, J1042, is in fact unable to terminate pregnancy in both guinea pigs and rats.[6] SPRMs exert only marginal effects on cervical ripening in guinea pigs during late pregnancy (K. Chwalisz, unpublished data). Collectively, these data strongly suggest that the SPRMs would not be suitable to terminate pregnancy in primates.

Effects of SPRMs on Ovulation and Ovarian Steroid Secretion

Comparative ovulation inhibition studies with progesterone antagonists and SPRMs in rats, guinea pigs, and primates show species-specific differences in the mechanism of progesterone action.[6,14,15] The macaque model seems to be the most suitable one to predict effects of SPRMs and antiprogestins on the ovarian and menstrual cycle. Paradoxically, both progestins and progesterone antagonists can inhibit ovulation in primates, acting most likely at different regulatory levels. Significantly, in primates, neither progesterone antagonists[17] nor SPRMs[16] suppress ovarian estrogen production, suggesting that these compounds do not impair the early stages of folliculogenesis. Our studies in cynomolgus monkeys with J1042 suggest that, in comparison with pure antiprogestins, SPRMs show stronger effects on the endometrium than on the hypophyseo-ovarian axis. In nonhuman primates, the anti-ovulatory activity of SPRMs is somewhat variable, which is in contrast to pure progesterone antagonists showing high inhibitory effects on ovulation.[15,16,18]

EFFECTS OF SPRMs ON THE PRIMATE ENDOMETRIUM

The primate endometrium represents a unique tissue with regard to vascular changes during the cycle and differs in this respect from that of other species such as rodents. If implantation does not occur, the upper part of the endometrium, the functionalis, is shed during menstruation in response to progesterone withdrawal at the end of the luteal phase. This effect is induced by the contraction of endometrial spiral arteries unique to primates. Cyclic changes of the endometrial blood vessels such as their damage during menstruation, neovascularization, and an increase in the growth and number of blood vessels occur within a single month. In humans, maximum growth and coiling of spiral arteries are observed during the secretory phase, an effect that is accompanied by an increased angiogenic activity.[19] Since similar cyclic changes are observed in the macaque endometrium,[20] studies in menstruating old-world monkeys such as cynomolgus or rhesus monkeys seem to be most relevant to humans.

The Endometrial Antiproliferative Effect of SPRMs and Progesterone Antagonists

Data from studies in nonhuman primates demonstrate that both SPRMs and progesterone antagonists are capable of suppressing endometrial growth at high

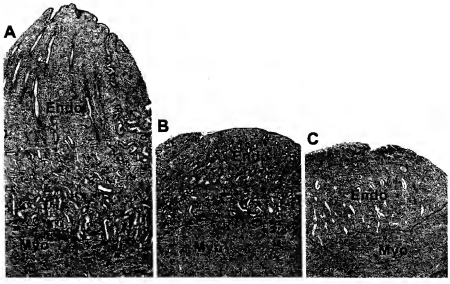


FIGURE 4a. Low-power micrographs of paraffin-embedded, hematoxylin/eosin-stained endometrial sections from cynomolgus macaques treated with vehicle (A), J1042 (B), or ZK 230 211 (C). Naturally cycling animals were treated on cycle days 2–22, and endometria were removed on day 23. Vehicle-treated monkeys revealed a typical progestational state marked by stromal expansion and glandular saculation (A), while monkeys treated with the SPRM (B) and antiprogestin (C) showed a striking reduction in endometrial thickness with compacted stroma. Original magnification: 25×. [Figure reduced to 75%.]

estradiol blood concentrations. The suppression of endometrial growth was first observed after treatment with RU 486 at relatively high doses.[21–23] This unexpected effect was initially termed "noncompetitive antiestrogenic effect".[21,22] Since the inhibitory effects of progesterone antagonists and SPRMs are specific to the endometrium, we therefore prefer the term "endometrial antiproliferative effects". More recent studies in nonhuman primates show that newer antiprogestins such as ZK 137 316 and ZK 230 211 are capable of inducing endometrial antiproliferative effects at very low doses.[15,17,18] In monkeys, progesterone antagonists typically reduced endometrial thickness, induced degeneration of endometrial glands, inhibited mitotic activity in the endometrial epithelium, and induced stromal compaction. Paradoxically, these effects were accompanied by increased endometrial expression of ER and PR, which indicates that not all estrogenic responses in the primate endometrium were inhibited by this treatment.[17]

Our recent study shows that SPRMs can also exert endometrial antiproliferative effects on the primate endometrium.[16] This study compared the treatment effects of the progesterone antagonists ZK 230 211 and ZK 137 316 with those of the most-agonistic SPRM, J1042, in intact cynomolgus monkeys. All three compounds exhibited a similar profound inhibitory effect on endometrial growth, characterized by low endometrial thickness and the absence of mitotic activity, and induced a distinct stromal compaction (FIG. 4a) (also see FIG. 4b). In summary, the studies reviewed

above demonstrate that both SPRMs and progesterone antagonists are capable of suppressing estrogen-induced endometrial growth. Within the reproductive tract, this effect seems to be endometrium-specific since no inhibition of estrogen responses could be observed in other organs such as the vagina and oviducts.[15]

More recently, inhibitory effects of SPRMs on mammary gland development could also be observed in a 39-week toxicological study with J867 in female cynomolgus monkeys after oral administration (R. Garg, unpublished data). FIGURE 5 shows the mammary gland morphology of a representative female monkey treated with J867. These effects were consistently observed in all animals exposed to J867 doses, producing an AUC (area under the curve) of 16.81 μg × h/mL or higher. This observation indicates that SPRMs have the potential to suppress both the endometrium and the mammary gland. It remains to be investigated whether this effect (1) is due to the inhibition of estrogen or progesterone effects in the mammary gland and (2) occurs at lower doses. It is well established that both progesterone and estrogen exhibit mitogenic activity on the primate mammary gland.

The exact mechanism of the endometrial antiproliferative effect is still unknown. At least four mechanisms are currently under consideration: (i) blockade of progesterone action on growth and function of spiral arteries;[15] (ii) suppression of the proliferative estrogen effects, specifically the mitotic activity of the endometrial glands via reduction of endometrial blood supply (vascular hypothesis);[15] (iii) down-regulation of stromal growth factors; and (iv) induction of androgen receptor (AR) expression in the endometrium.[24]

Major progress in understanding the mechanism of action of both antiprogestins and SPRMs on the primate endometrium could be achieved by including full-thickness endometrial biopsies in the morphological evaluation.[17] These studies demonstrated profound inhibitory effects of progesterone antagonists on spiral arteries, which showed either perivascular degeneration or inhibition of growth depending on the dose and duration of treatment. After treatment with the reference SPRM, J1042, however, the endometrial glands were not degenerated and showed residual secretory activity suggestive of partial agonistic activity. Interestingly, the number of spiral arteries and their diameter were similarly reduced after treatment with both antiprogestins (ZK 137 316, ZK 230 211) and J1042 (FIG. 4b).[16] The perivascular hyalinization and degenerative changes were only observed, though, in animals treated with antiprogestins. Hence, compared to the pure antiprogestins, J1042 seems to exhibit "milder" inhibitory effects on the endometrium, an effect that can be explained by the presence of mixed agonistic/antagonistic activities at PR.

Based on these results, we proposed that the endometrial antiproliferative effect of progesterone antagonists and SPRMs might be primarily due to the degeneration (pure progesterone antagonists) or inhibition (SPRMs) of spiral arteries. In addition, both of these classes of PR ligands may inhibit endometrial angiogenesis (FIG. 6).[15] This hypothesis would explain why both amenorrhea and endometrial atrophy can occur, even though there is an increased expression of some estrogen molecular markers in the functionalis—for example, ER and PR. The exact mechanisms underlying the degenerative changes in spiral arteries following treatment with progesterone antagonists and inhibitory effects on their function and growth by SPRMs are still unknown. There is evidence from studies in baboons that progesterone antagonists inhibit the expression of the inducible nitric oxide synthase isoform (iNOS) in the luteal phase endometrium, particularly in the stromal cells around the spiral

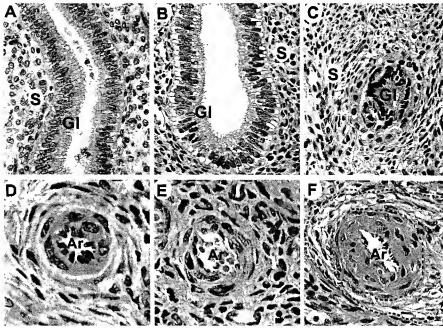


FIGURE 4b. High-power micrographs of paraffin-embedded, hematoxylin/eosin-stained endometrial sections. The vehicle-treated endometrium (panels A and D) revealed typical midluteal phase endometrial histology as evidenced by an expanded stroma (S), columnar glandular epithelium (Gl), and normal spiral arteries (Ar). Monkeys treated with J1042 (panels B and E) showed stromal compaction; however, glandular epithelium was columnar and secretory, and there were no marked degenerative changes in spiral arteries. ZK 230 211 treatments caused severe stromal compaction (panel C), pronounced degenerative changes in the glands (panel C), and signs of periarteriolar degeneration (panel F; periarteriolar zone within the two dotted lines). Original magnification: panels A–C, 312×; panels D–F, 937×. [Figure reduced to 75%.]

arteries.[25] Moreover, progesterone antagonists may alter endometrial vascular endothelial growth factor (VEGF) synthesis and other angiogenic factors, thus inhibiting angiogenesis.

Very recently, a new mechanism of endometrial antiproliferative effects of antiprogestins has been proposed based on studies of AR expression in the monkey and human endometrium exposed to antiprogestin treatment.[24] This study shows that various progesterone antagonists can dramatically induce AR expression in endometrial glands and can enhance its expression in endometrial stroma. Physiologically, AR is weakly expressed in stromal cells of the primate endometrium. Since there is substantial evidence that exogenous androgens can have inhibitory effects on the female reproductive system, including the induction of endometrial atrophy,[26–28] this mechanism may contribute to the endometrial antiproliferative effects of progesterone antagonists and SPRMs. The effects of SPRMs on AR expression still remain to be studied.

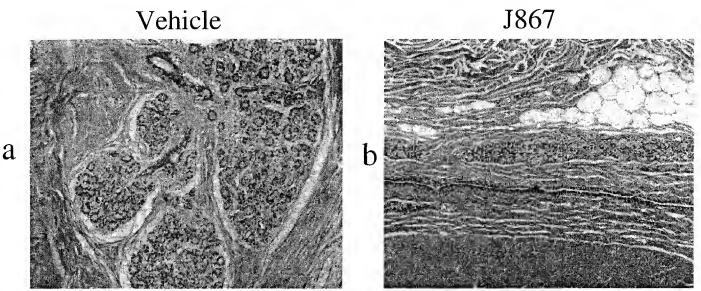


FIGURE 5. Micrograph of paraffin-embedded, hematoxylin/eosin-stained representative mammary gland section from cynomolgus macaques orally treated with high-dose J867 for 39 weeks: **(a)** vehicle control; **(b)** J867 treatment. Original magnification: 150×. [Figure reduced to 85%.]

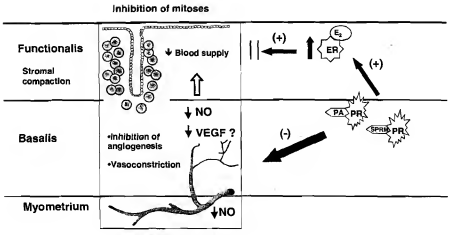


FIGURE 6. Proposed model of action of SPRMs and PAs on the primate endometrium. Inhibition or damage of spiral arteries in the basalis seems to be the primary effect of PAs and SPRMs. This effect may be due to several factors, including the downregulation of NOS leading to local NO deficiency and vasoconstriction, the inhibition of VEGF synthesis in epithelial and stromal compartments, and the general suppression of endometrial stroma. Terms: PA, progesterone antagonist; SPRM, selective progesterone receptor modulator; VEGF, vascular endothelial growth factor; NO, nitric oxide; E_2, estradiol. (Modified from reference 6, with permission from *Steroids*.)

Effects on Uterine Bleeding

The SPRMs have a potential to reversibly induce amenorrhea by selectively targeting the endometrium even in the presence of ovulation. Such an effect cannot be achieved with progestins since they inevitably produce breakthrough bleeding. The pure progesterone antagonists can also suppress menstruation in nonhuman primates.[15,18] However, the progesterone antagonist doses inhibiting ovulation and suppressing menstruation are very similar. Therefore, these compounds are not dissociated with regard to endometrial and central/ovarian effects. The presence of agonistic activity results in dissociation of these effects.

SPRMs AND UTERINE PROSTAGLANDINS

The effects of SPRMs on uterine prostaglandins may be clinically meaningful since these proinflammatory mediators are implicated in dysmenorrhea and the control of uterine blood flow. The first evidence that PR ligands directly control uterine prostaglandins came from studies in cycling guinea pigs.[12,14] It is well established in guinea pigs and some other species such as rabbits that the uterine prostaglandins are responsible for luteolysis. Hysterectomy prevents luteolysis, which results in the pro-

longation of the corpus luteum life span in these species. Surprisingly, treatment with progesterone antagonists prevented luteolysis in guinea pigs. This effect could be blocked with the pure progestin, R 5020.[6,14] Importantly, a prolongation of the duration of luteal phase was accompanied by a complete inhibition of uterine PGF2α secretion. Based on these experiments, it was proposed that progesterone is the major stimulator of uterine prostaglandins in the nonpregnant uterus, an effect that can be blocked at the uterine level by antiprogestins.[14] During pregnancy, the control of uterine prostaglandins seems to be more complex, with placental factors playing most likely the dominant role. More recently, the inhibition of luteolysis test in cycling guinea pigs was used to quantify the agonistic and antagonistic activities of SPRMs.[6]

The luteolysis in primates is not controlled by uterine factors. Some fundamental mechanisms related to progesterone regulation of uterine prostaglandin secretion may, however, be similar in guinea pigs and primates. The uterine cyclooxygenase isoforms (COX), the rate-limiting enzymes that catalyze the initial step in the formation of PGs from arachidonic acid, may represent a target for PR ligands. Other recent studies with the progesterone antagonist, ZK 137 316, performed in cycling and early pregnant baboons show that the constitutive isoform COX-1 is primarily regulated by progesterone, whereas regulation of the inducible isoform COX-2 may involve additional factors of embryonic origin.[29] Treatment of cycling baboons with ZK 137 316 during the luteal phase dramatically inhibited COX-1 expression in the endometrial epithelium, whereas it induced COX-2 expression in the stromal cells. With the onset of pregnancy, COX-1 expression in epithelial cells decreased dramatically, while COX-2 continued to be detected.

The effects of SPRMs on the uterine COX expression still have to be studied in the primate uterus. However, in view of the similarities between SPRMs and progesterone antagonists with regard to endometrial effects, SPRMs have a potential to inhibit uterine prostaglandins and perhaps to suppress perimenstrual pain.

CONCLUDING REMARKS AND CLINICAL IMPLICATIONS

The studies in macaques reviewed above indicate that, unlike progestins, the SPRMs have the potential to selectively suppress estrogen-dependent endometrial growth and to induce a reversible amenorrhea without adverse systemic effects of estrogen deprivation. These properties provide the rational basis for the treatment of endometriosis. Our studies indicate that the spiral arteries, which are unique to the primate endometrium, are the primary targets damaged or functionally inhibited by antiprogestins and SPRMs, respectively. The inhibitory effects of SPRMs on these unique vessels may underlie the paradoxical, endometrium-specific antiproliferative effects of these compounds. The stabilization (prevention of unscheduled bleeding) of the endometrial vessels may represent one of the major advantages of SPRMs compared to progestins. It is well known that chronic progestin treatment increases the fragility of endometrial blood vessels, leading to breakthrough bleeding. In addition, SPRMs have a potential of alleviating painful symptoms, the major clinical problem in endometriosis. Furthermore, SPRMs have a potential of controlling the progression of the disease by acting directly on the lesions. Since the ovarian estrogen production is maintained during SPRM treatment, the vasomotor symptoms and skeletal side effects related to estrogen deficiency may not occur (TABLE 2).

TABLE 2. Rationale for using SPRMs in the treatment of endometriosis

Pharmacodynamic effects
Reversible suppression of menstruation (endometrial bleeding) via a direct effect on endometrial blood vessels.
Selective inhibition of endometrial proliferation without systemic effects of estrogen deprivation.
Inhibition of uterine prostaglandins and potential pain relief.
Inhibition of ovarian progesterone secretion in the absence of estrogen deprivation.
No stimulatory effects on the mammary gland.

Other emerging technologies for the treatment of endometriosis such as selective estrogen receptor modulators (SERMs) and aromatase inhibitors are emerging. The goal of these treatments is to inhibit estrogen effects in the ectopic endometrium (SERMs) or to reduce ovarian and local estrogen production (aromatase inhibitors). The SERM raloxifene was reported to be effective in both a surgically prepared rat uterine explant model and in rhesus macaques with spontaneous endometriosis.[30] A rationale for the treatment of this condition with aromatase inhibitors is provided by recent clinical studies demonstrating that aromatase, a key enzyme of estrogen biosynthesis, is aberrantly overexpressed in endometriosis and by a casuistic observation reporting the efficacy of the aromatase inhibitor anastrozole.[31] The aromatase inhibitors may require add-back therapy to protect bones, whereas the currently available SERMs are known to stimulate gonadotropins and thereby may stimulate ovarian estrogen production. SPRMs may have some advantages over both SERMs and aromatase inhibitors since they show a high degree of endometrial selectivity in reducing estrogenic responses. Unfortunately, causative treatments of endometriosis are not yet available. As knowledge of endometriosis advances through the use of techniques from molecular biology, new concepts toward a causative therapy of endometriosis based on novel therapeutic targets may be developed in the future.

In conclusion, SPRMs represent a new opportunity in the treatment of endometriosis and other gynecological disorders. The discovery that SPRMs with either reduced or absent abortifacient activity exert inhibitory effects on the primate endometrium in terms of growth suppression, creation of reversible amenorrhea, and potential to control pain is exciting and deserves clinical study. It remains to be established in clinical trials whether SPRM therapy is superior to the current medical treatment strategies of endometriosis, which still remains, for both physician and patient, one of the most frustrating of women's diseases.

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